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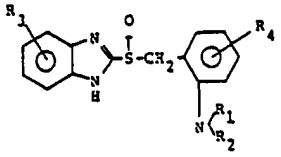
(54) Benzimidazole derivatives

(57) Benzimidazole derivatives of the formula



(where R_1 is hydrogen, C_{1-8} alkyl, cycloalkyl, phenyl or aralkyl, R_2 is hydrogen or C_{1-8} alkyl, or R_1 and R_2 together form a ring with the adjacent nitrogen atom, and R_3 and R_4 are hydrogen, halogen, trifluoromethyl, alkyl, alkoxy, alkoxycarbonyl or amino) are antiulcer agents.

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SPECIFICATION

Benzimidazole derivatives, process for preparing the same and antiulcer agents containing the same

This invention relates to novel benzimidazole derivatives, to a process for preparing such derivatives and to antiulcer agents containing such derivatives.

As is well known in the art to which the present invention relates, $H^+ + K^+$ATPase plays a principal role in the final secretion mechanism of gastric acid in stomach cells [Scand. J. Gastroenterol., *14*, 131–135 (1979)]. Norinium bromide is known as a substance having $H^+ + K^+$ATPase inhibitory activity [Proceeding of the Society for Experimental Biology and Medicine, *172*, 308–315 (1983)].

On the other hand, 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole [Omeprazole] has been developed as an antiulcer compound having $H^+ + K^+$ATPase inhibitory activity [Am. J. of Physiol., *245*, G64–71 (1983)].

There is a keen demand for new compounds having a more enhanced effect on $H^+ + K^+$ATPase inhibition than these known compounds.

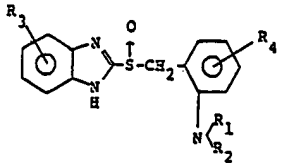
With the foregoing in view, the present Applicants have conducted extensive research and have now found that certain benzimidazole derivatives exhibit excellent suppressive effects against the secretion of gastric acid owing to their specific $H^+ + K^+$ATPase inhibitory effects, coupled with cytoprotective action.

It is an object of the present invention, therefore, to provide new benzimidazole derivates which are useful for antiulcer purposes.

Another object of the invention is to provide a novel process for preparing such benzimidazole derivatives.

Still another object of the invention is to provide antiulcer agents containing such benzimidazole derivatives as an effective component thereof.

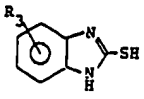
According to a first aspect of the present invention, there is provided benzimidazole derivatives represented by the formula (I),



(I)

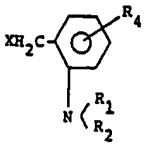
where R_1 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms, or a cycloalkyl, phenyl or aralkyl group; R_2 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms; or R_1 and R_2 together form a ring with the adjacent nitrogen atom; and R_3 and R_4 are in each case a hydrogen or halogen atom, or a trifluromethyl, lower alkyl, lower alkoxy, lower alkoxycarbonyl or amino group, and may be the same or different.

According to a second aspect of the invention there is provided a process for preparing a benzimidazole derivative as specified above, which comprises reacting a 2-mercaptobenzimidazole represented by the formula (II),



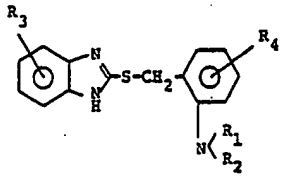
(II)

where R_3 is as defined above, with a 2-aminobenzyl compound represented by the formula (III),



(III)

where R_1, R_2 and R_4 are as defined above and X is a reactive group, thereby forming a compound represented by the formula (IV),

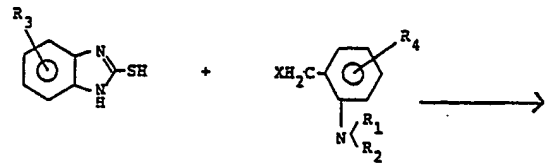


(IV)

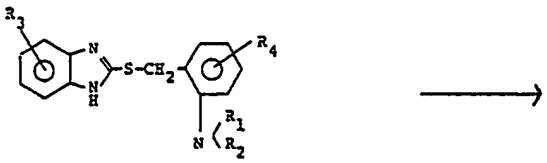
where R_1, R_2, R_3 and R_4 are as defined above, and then oxidizing the compound of the formula (IV).

According to a third aspect of the invention, there is provided an antiulcer agent comprising as an effective component thereof, a benzimidazole derivative as specified above.

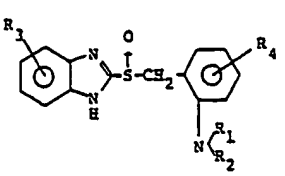
Benzimidazole derivatives of the formula (I) according to the present invention may be prepared, for example, by reacting a 2-mercaptobenzimidazole of the formula (II) with a 2-aminobenzyl compound of the formula (III) to form a compound of the formula (IV) and then oxidizing the compound (IV) in accordance with the following reaction scheme:–



(II) (III)



(IV)



(I)

where X is a reactive group and R_1 to R_4 inclusive are as defined previously.

The starting compound (II) useful for a process according to the invention is already known in the art. The compound (II) may be prepared, for example, by the process described in Org. Synth., *30*, 56. The reactive group X in the other starting compound (III) may be a halogen atom, such as chlorine or bromine, or a sulfonyloxy group such as a methylsulfonyloxy or toluenesulfonyloxy group. The compound (III) in which a chlorine atom is bonded as X may be prepared, for example, by the process disclosed in J. Chem. Soc., 98–102 (1942). Both of these starting compounds can also be in the form of salts.

The reaction between the compound (II) and the compound (III), or between their respective salts, may be effected by stirring them in an inert solvent, such as toluene, benzene, ethanol or acetone, at a temperature of from room temperature to the refluxing temperature, for 30 minutes to 24 hours. In such case, it is preferred to have an alkaline compound such as NaOH, KOH, K_2CO_3 or $NaHCO_3$ present in the reaction system, so that the resulting acid can be neutralised.

The compound (IV) may be converted to its corresponding oxo compound by any method known *per se*. For example, this conversion may be achieved by oxidizing the compound (IV) with an oxidizing agent, for example, an organic peracid such as m-chloroperbenzoic acid, hydrogen peroxide, sodium hypochlorite or sodium metaperiodate. The reaction may be effected

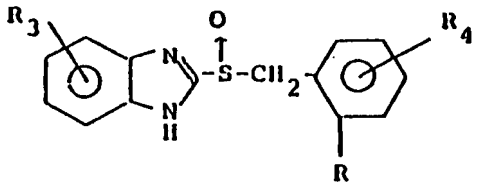
in an inert solvent such as chloroform, dichloromethane, methanol or ethyl acetate, at −30 to +50°C, preferably at −15 to +5°C.

The pharmacological effects of some compounds typical of the invention were tested. The test results are given below.

(1) $H^+ + K^+$ATPase inhibitory effects:

Following the method of Forte et al [J. Applied Physiol., *32*, 714–717 (1972)], gastric acid secretory cells of a rabbit gastric mucosa were isolated and vesicle containing $H^+ + K^+$ATPase was prepared by centrifuging the cells in Ficoll of discontinuous density gradient. After the enzyme was incubated at room temperature for 25 minutes in 0.5 ml of a solution which contained 5 mM of an imidazole buffer (pH 6.0) and 2×10^{-4} M of each test compound, the mixture was heated to 37°C at which it was allowed to stand for further 5 minutes. To the mixture was added 0.5 ml of a solution which contained 4 mM of magnesium chloride, 80 mM of an imidazole buffer (pH 7.4), 20 mM of potassium chloride and 4 mM of ATP. The resulting mixture was reacted at 37°C for 15 minutes and 1 ml of a 24% solution of trichloroacetic acid was then added to terminate the reaction. The inorganic phosphorus liberated was quantitatively analyzed by the method proposed by Taussky and Shorr [J. Biol. Chem., *202*, 675–685 (1953)]. The K^+-dependent activity of the ATPase was determined by subtracting its activity obtained when no potassium chloride was contained. The results are summarized in Table 1 in which Inventive compounds 1 to 19 are the compounds obtained in several of Examples 1 to 26 and Comparative compound 1 is the compound obtained in Reference Example 1, all of which examples are set out below.

Table 1



Test compound	R	R_3	R_4	$H^+ + K^+$ ATPase inhibitory effect (%)
Comparative compound 1	H	H	H	0
Inventive compound 1	NH_2	H	H	88.2
Inventive compound 2	$NHCH_3$	H	H	100
Inventive compound 3	$N(CH_3)_2$	H	H	100
Inventive compound 4	$N(CH_3)_2$	$5\text{-}OCH_3$	H	100
Inventive compound 5	$N(CH_3)_2$	$5\text{-}COOCH_3$	H	97.9
Inventive compound 6	$N(CH_3)_2$	$5\text{-}CH_3$	H	100
Inventive compound 7	$N(CH_3)_2$	5-Cl	H	100
Inventive compound 8	$N(CH_3)_2$	$5\text{-}CF_3$	H	100

Table 1 (cont'd)

Test compound	R	R_3	R_4	$H^+ + K^+$ ATPase inhibitory effect (%)
Inventive compound 9	$N(CH_3)_2$	$4\text{-}CH_3$	H	100
Inventive compound 10	$N(CH_3)_2$	H	$6\text{-}CH_3$	100
Inventive compound 11	$N(CH_3)_2$	H	4-Cl	100
Inventive compound 12	$N(CH_3)_2$	H	$5\text{-}OCH_3$	100
Inventive compound 13	$N(CH_3)_2$	H	$5\text{-}CH_3$	100
Inventive compound 14		H	H	82.3
Inventive compound 15		H	H	100
Inventive compound 16		H	H	100
Inventive compound 17		H	H	66.7
Inventive compound 18		H	H	77.9
Inventive compound 19		H	H	100

(2) Inhibitory effects against the secretion of gastric acid:

Male Donryu rats were used which had a body weight of 200 to 250 g and fasted (while allowing free access to water) for 24 hours in accordance with the usual method [Shay, H. et al, Gastroenterology, *5*, 43–61 (1945)]. Under ether anesthesia the pylorus was ligated and each test compound was administered intraduodenally. Four hours later, each rat was killed and the stomach was removed to collect the gastric juice. The inhibitory effect was determined by comparing the acid output which was obtained by titration to pH 7.0 with 0.1–N NaOH by means of an automatic titrator, with the corresponding value of a control rat prepared in the same manner except that a vehicle alone was administered. The results are given in Table 2.

Table 2

Test compound	Dose (mg/kg)	Suppresive effect against secretion of gastirc acid (%)
Comparative compound 1	100	44
Cimetidine	100	80.3
	30	59.1
	10	25.3
Inventive compound 3	100	99.3
	30	94.3
	10	62.9
Inventive compound 7	100	77.5
Inventive compound 9	100	95.7
Inventive compound 10	100	98.7
Inventive compound 11	100	72.8
Inventive compound 13	100	97.9
Inventive compound 15	100	91.5
	30	71.7
	10	48.8

(3) Inhibitory effects against four gastric lesion models:

Four different types of gastric lesion models were induced in male Donryu rats (180 to 240 g) which had been deprived of food but allowed free access to water for 24 to 48 hours prior to experiments.

a) Shay ulcers:

Under ether anesthesia the abdomen of each rat fasted for 48 hours was incised and the pylorus ligated. Fourteen hours later, the animal was killed and the stomach was examined for any ulcer in the forestomach. Each test compound or a vehicle alone was given intraduodenally in a volume of 0.2 ml/100 g body weight immediately after pylorus ligation.

b) Water-immersion stress-induced erosions:

Rats fasted for 24 hours before experiments were placed in a restraint cage. The animals were immersed vertically to the level of the xiphoid process in a water bath (21°C) for 7 hours and then killed. The stomach of each rat was removed and inflated by injecting 10 ml of 1% formalin to fix the inner and outer layers of the gastric walls. This formalin treatment was performed in all of the following experiments. Subsequently, the stomach was incised along a greater curvature and examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 10 minutes before stressing.

c) Indomethacin-induced erosions:

Indomethacin suspended in a 0.2% CMC solution was given subcutaneously to rats in a dose of 25 mg/kg, which rats had been fasted for 24 hours before experiments. Seven hours later, each animal was killed and the stomach was examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 10 minutes before indomethacin treatment.

d) HCl-EtOH-induced erosions:

A hydrochloric acid-ethanol solution (150 mM HCl in 60% EtOH) was given orally to rats in a dose of 1 ml/200 g, which rats had been fasted for 24 hours before experiments. One hour later, each animal was killed and the stomach was examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 30 minutes before ethanol treatment.

The results are shown in Table 3-A to Table 3-D.

Table 3-A

a) Shay ulcers

Test compound	mg/kg id	Inhibition (%)
Inventive compound 3	3	28
	10	68
	30	69
Cimetidine	100	−29
	300	44

Table 3-B

b) Water-immersion stress-induced erosions

Test compound	mg/kg po	Inhibition (%)
Inventive compound 3	30	69
	100	97
" 4	30	27
	100	95
" 10	30	39
	100	91
" 12	30	41
	100	74
" 13	30	64
	100	88
Cimetidine	60	49
	200	87

Table 3-C

c) Indomethacin-induced erosions

Test compound	mg/kg po	Inhibition (%)
Inventive compound 3	30	7.0
	100	88
Cimetidine	30	39
	100	76

Table 3-D

d) HCl-EtOH-induced erosions

Test compound	mg/kg po	Inhibition (%)
Inventive compound 3	10	89
	30	100

(4) Acute toxicity test:

To male Wistar rats having a body weight of 80 to 90 g were intraperitoneally administered suspensions of certain inventive compounds which had been suspended in 0.2% CMC physiological saline. The rats were observed for 7 days. The results are shown in Table 4.

Table 4

Inventive compound	LD_{50}
10	600 mg/kg or more
12	500 - 600 mg/kg
13	600 mg/kg or more
18	300 mg/kg or more
19	300 mg/kg or more

Moreover, male ICR mice having a body weight of 23 to 26 g were orally administered with Inventive compound 3. The mice were then observed for 3 days. The MLD was found to be 1,000 mg/kg or more.

The compounds (I) of the present invention may be administered either orally or parenterally. Preparation forms for oral administration may include for example tablets, capsules, powder, granules, and syrup. Preparation forms for parenteral administration include injectable preparations and the like. For the formulation of these preparations, there may be used excipients, disintegrants, binders, lubricants, pigments, diluents and like materials, such as are commonly employed in the art. The excipients may include dextrose, lactose and the like. Starch, carboxymethylcellulose and the like may be used as the disintegrants. Magnesium stearate, talc and the like may be used as the lubricants. The binders may be hydroxypropylcellulose, gelatin, polyvi-

nylpyrrolidone and the like.

The dose may usually be about 1 mg/day to 50 mg/day in the case of an injectable preparation and about 10 mg/day to 500 mg/day in the case of oral administration, both for an adult. The dose may be either increased or decreased depending on the age and other conditions.

The following reference and specific examples are given to further illustrate the present invention, but it is to be noted that the invention is not limited thereto.

Reference Example 1

(1) 2-Benzylthiobenzimidazole:

To a solution containing 1.47 g of NaOH dissolved in a mixed solvent consisting of 5 ml of water and 50 ml of ethanol were added 5 g of 2-mercaptobenzimidazole and 4.2 g of benzyl chloride. The resulting solution was heated under reflux for one hour. The reaction mixture was poured into ice water and crystals precipitated were collected by filtration to give 7.7 g of crude crystals (96%). The crystals were recrystallized from ethanol to obtain 5.9 g of 2-benzylthiobenzimidazole as colorless needles. m.p. 184°C.

(2) 2-Benzylsulfinylbenzimidazole (Comparative compound 1):

In 30 ml of chloroform was dissolved 4.5 g of 2-benzylthiobenzimidazole, followed by gradual addition of 4.6 g of m-chloroperbenzoic acid (purity: 70%) at temperatures below 0°C. The mixture was stirred for 20 minutes and crystals deposited were then collected by filtration. The filtrate was washed successively with a saturated $NaHCO_3$ solution, sodium thiosulfate and saturated brine and the filtrate thus washed was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give 4.3 g of crude crystals. The crystals were recrystallized from ethanol to obtain 2.0 g of 2-benzylsulfinylbenzimidazole as colorless crystals. m.p. 169–170°C.

Example 1

(1) 2-(2-Aminobenzylthio)benzimidazole:

In 40 ml of ethanol were dissolved 1.8 g of 2-aminobenzyl chloride hydrochloride and 1.5 g of 2-mercaptobenzimidazole. While shielding light, the resulting solution was stirred at room temperature for 23 hours. Powder precipitated was collected by filtration. After being washed successively with ethanol and ether, the powder was recrystallized from a mixed solvent of methanol and ether to obtain 1.8 g of 2-(2-aminobenzylthio)benzimidazole hydrochloride as colorless granular crystals. m.p. 207°C (decomposed).

(2) 2-(2-Aminobenzylsulfinyl)benzimidazole (Inventive compound 1):

One gram of 2-(2-aminobenzylthio)benzimidazole hydrochloride was dissolved in ice water. The solution was neutralized with 512 mg of sodium bicarbonate, followed by extraction with chloroform. The resulting chloroform solution was washed with saturated brine. After drying the chloroform solution with anhydrous sodium sulfate, the solvent was distilled off under reduced pressure at room temperature. Thereafter, 0.5 g of the thus obtained 2-(2-aminobenzylthio)benzimidazole was dissolved in a mixed solvent which consisted of 30 ml of chloroform and 3 ml of methanol. The resulting solution was chilled to −10°C and added little by little with 0.4 g of m-chloroperbenzoic acid (purity: 70%). The mixture was then stirred at the same temperature for 10 minutes. Light yellowish powder precipitated was collected by filtration. After being washed with ether, the powder was recrystallized from a mixed solvent of methanol and ether to obtain 0.33 g of 2-(2-aminobenzylsulfinyl)benzimidazole as white crystalline powder. m.p. 150°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3200, 1440, 1400, 1260, 1035

^1H–NMR ($CDCl_3$) δ:

4.40 and 4.64 (each d, 2H, J=14HZ,

–SCH_2–), 6.24–7.80 (m, 8H, aromatic protons)

Example 2

(1) 2-(2-Methylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (1.8 g) and 2-methylaminobenzyl chloride hydrochloride (2.5 g) in 10 ml of ethanol were stirred at room temperature for 30 minutes. Ten milliliters of ether was added and crystals precipitated were collected by filtration. The crystals were washed with ether to give 3.5 g of 2-(2-methylaminobenzylthio)benzimidazole hydrochloride (85%). The crystals

were suspended in ethyl acetate and then neutralized by addition of a saturated $NaHCO_3$ solution. After being washed with brine, the organic layer was dried with anhydrous sodium sulfate. After distilling off the solvent under reduced pressure, the residue was recrystallized from acetonitrile to obtain 1.87 g of 2-(2-methylaminobenzylthio)benzimidazole as colorless crystals. m.p. 107–108°C.

(2) 2-(2-Methylaminobenzylsulfinyl)benzimidazole (Inventive compound 2):

2-(2-Methylaminobenzylthio)benzimidazole (1.0 g) was dissolved in 20 ml of chloroform. After chilling the solution to −10°C, 0.87 g of m-chloroperbenzoic acid (purity: 70%) was added little by little. After being stirred at the same temperature for 10 minutes, the mixture was washed successively with a saturated $NaHCO_3$ solution and saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was recrystallized from acetonitrile to obtain 0.43 g of 2-(2-methylaminobenzylsulfinyl)benzimidazole as white crystalline powder. m.p. 122.5–124°C.

IR ν_{max}^{KBr} cm^{-1}: 3220, 1600, 1500, 1435, 1400, 1305, 1265, 1045

^{1}H–NMR ($CDCl_3$)δ:

2.52 (s, 3H, $-NCH_3$), 4.36 and 4.60 (each d, 2H, J=16HZ,

$-SCH_2-$), 6.30–7.80 (m, 8H, aromatic protons)

Example 3

(1) 2-(2-Dimethylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (4.73 g) was dissolved in 150 ml of ethanol, followed by addition of 6.18 g of 2-dimethylaminobenzyl chloride hydrochloride. The mixture was stirred at room temperature for 30 minutes. Crystals precipitated were collected by filtration. A saturated $NaHCO_3$ solution was added to the crystals, followed by extraction with chloroform. The chloroform layer was washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was recrystallized from a mixed solvent of chloroform and acetonitrile to obtain 5.39 g of 2-(2-dimethylaminobenzylthio)benzimidazole as colorless crystals. m.p. 164°C.

(2) 2-(2-Dimethylaminobenzylsulfinyl)benzimidazole (Inventive compound 3):

(a) 2-(2-Dimethylaminobenzylthio)benzimidazole (4.8 g) was dissolved in a mixed solvent which consisted of 40 ml of chloroform and 5 ml of methanol. After chilling the solution to 0°C, 3.86 g of m-chloroperbenzoic acid (purity: 70%) was added little by little. Ten minutes later, a saturated $NaHCO_3$ solution was added to the reaction mixture, followed by extraction with chloroform. The chloroform solution was washed with saturated brine and then dried with anhydrous sodium sulfate. The chloroform was distilled off under reduced pressure and the residue was recrystallized from a mixed solvent of chloroform and ether to obtain 2.97 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as colorless crystals. m.p. 112°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3170, 1485, 1435, 1400, 1260, 1040

^{1}H–NMR ($CDCl_3$)δ:

2.62 (s, 6H, $>N(CH_3)_2$), 4.47 and 4.87 (each d, 2H, J=14Hz,

$-SCH_2-$), 6.70–7.90 (m, 8H, aromatic protons), 12.16 (br., 1H, $>NH$)

(b) 2-(2-Dimethylaminobenzylthio)benzimidazole (400 g) was dissolved in methylene chloride (1.06 l)—methanol (1.06 l). Acetic acid (212 ml) was added to the solution and the mixture was stirred until the solid was dissolved completely. After cooling the resulting solution to 2 to 5°C, 182 ml of 35% hydrogen peroxide, 123 ml of water and 8.83 g of ammonium metavanadate were added. The reaction mixture was stirred at 2 to 5°C for 9 hours. The reaction was quenched with a 20% $NaHCO_3$ solution. The organic layer was separated, washed with an aqueous $Na_2S_2O_3$ solution and with saturated brine and then dried with anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure and the residue was recrystallized from acetonitrile to obtain 317 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as colorless crystals.

(c) 2-(2-Dimethylaminobenzylthio)benzimidazole (10 g) was dissolved in a 20% NaOH solution (30 ml) and ethyl acetate (120 ml). After cooling the solution with ice water, a mixture of 70 ml of 12% NaOCl and 30 ml of 20% NaOH was added dropwise at 3 to 5°C over 80 minutes. The reaction mixture was stirred for one hour at the same temperature as just referred to. The reaction was quenched with a 10% $Na_2S_2O_3$ solution and the organic layer was washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was recrystallized from acetonitrile to obtain 7.9 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as colorless crystals.

Example 4

(1) 2-(2-Dimethylaminbenzylthio)-5-methoxybenzimidazole:

2-Mercapto-5-methoxybenzimidazole (2.70 g) was dissolved in 60 ml of ethanol, followed by addition of 3.09 g of 2-dimethylaminobenzyl chloride hydrochloride. The resulting mixture was stirred at room temperature for 30 minutes. Crystals precipitated were collected by filtration. A saturated $NaHCO_3$ solution was added to the crystals, followed by extraction with chloroform. The chloroform solution was washed with saturated brine and then dried with anhydrous sodium sulfate. The chloroform was distilled off under reduced pressure to obtain 3.85 g of 2-(2-dimethylaminobenzylthio)-5-methoxybenzimidazole as a colorless oily matter.

(2) 2-(2-Dimethylaminobenzylthio)-5-methoxybenzimidazole (2.43 g) was dissolved in a mixed solvent which consisted of 25 ml of chloroform and 2 ml of methanol. After chilling the solution to 0°C, 3.86 g of m-chloroperbenzoic acid (purity: 70%) was added little by little. Ten minutes later, a saturated $NaHCO_3$ solution was added to the reaction mixture, followed by extraction with chloroform. The chloroform solution was washed with saturated brine and then dried with anhydrous sodium sulfate, followed by removal of the chloroform by distillation under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol:50/1) and then recrystallized from a mixed solvent of ether and hexane to obtain 1.50 g of 2-(2-dimehtylaminobenzylsulfinyl)-5-methoxybenzimidazole as light yellowish crystals. m.p. 105°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3270, 1625, 1485, 1390, 1205, 1175, 1030

^{1}H–NMR ($CDCl_3$)δ:
2.63 (s, 6H, $-N(CH_3)_2$), 3.81 (s, 3H, $-OCH_3$),
4.48 and 4.85 (each d, 2H, J=15Hz,

$-SCH_2-$), 6.60–7.80 (m, 7H, aromatic protons),
12.16 (br., 1H, >N*H*)

Example 5

(1) 2-(2-Diethylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (50.0 g) was suspended in 500 ml of ethanol, followed by addition of 77.9 g of 2-diethylaminobenzyl chloride hydrochloride. The resulting mixture was stirred at room temperature for 30 minutes. Crystals precipitated were collected by filtration and added with a saturated $NaHCO_3$ solution, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was dissolved in ethanol. The resulting solution was treated with activated carbon. The activated carbon was removed by filtration and the ethanol by distillation under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate and hexane to obtain 88.7 g of 2-(2-diethylaminobenzylthio)benzimidazole as light brownish crystalline powder. m.p. 134–135°C.

(2) 2-(2-Diethylaminobenzylsulfinyl)bezimidazole:

2-(2-Diethylaminobenzylthio)benzimidazole (84.0 g) was dissolved in a mixed solvent which consisted of 600 ml of methylene chloride and 150 ml of methanol. After chilling the solution to 0°C, 79.8 g of m-chloroperbenzoic acid (purity: 60%) was added little by little. Ten minutes later, a saturated $NaHCO_3$ solution was added to the reaction mixture, followed by extraction with methylene chloride. The resulting methylene chloride solution was dried with anhydrous sodium sulfate. The methylene chloride was distilled off under reduced pressure and the residue was subjected to silica gel column chromatography (silica gel, 280 g; eluent, acetone:hex-

ane=1:2 v/v). The eluate was dissolved in a 1:8 v/v mixed solvent of ethanol and hexane and crystals precipitated were removed by filtration. The filtrate was concentrated under reduced pressure. The residue was recrystallized twice from isopropyl ether to obtain 32.3 g of 2-(2-diethylaminobenzylsulfinyl)benzimidazole as colorless crystals. m.p. 110.5–112°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3200, 2980, 1490, 1400, 1270, 1015, 765, 750

^{1}H–NMR ($CDCl_3$)δ:

1.01 (t, 6H, J=7Hz, $-CH_2CH_3\times2$)
3.00 (q, 4H, J=7Hz, $-CH_2CH_3\times2$)
4.46 and 4.97 (each d, 2H, J=13Hz,

O
↑
$-SCH_2-$), 6.80–7.90 (m, 8H, aromatic protons),
12.41 (br., 1H, >NH)

Example 6

(1) 2-(2-Dimethylaminobenzylthio)-4-methylbenzimidazole:

2-Dimethylaminobenzyl chloride hydrochloride (1.26 g) was added to a suspension of 1.0 g of 2-mercapto-4-methylbenzimidazole in 10 ml of ethanol. The resulting mixture was stirred at room temperature for 2 hours. Crystals precipitated were collected by filtration. After being washed successively with ethanol and ether, the crystals were dissolved in chloroform. The chloroform solution was neutralized with a saturated $NaHCO_3$ solution, washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and ether was added to the residue. Crystals precipitated were collected by filtration to obtain 13.8 g of 2-(2-dimethylaminobenzylthio)-4-methylbenzimidazole as white crystalline powder.

^{1}H–NMR ($CDCl_3$):δ

2.52 (s, 3H,), 2.84 (s, 6H), 4.36 (s, 2H),
6.8–7.6 (m, 7H)

(2) 2-(2-Dimethylaminobenzylsulfinyl)-4-methylbenzimidazole (Inventive compound 9):

2-(2-Dimethylaminobenzylthio)-4-methylbenzimidazole (1.1 g) was dissolved in 15 ml of chloroform, followed by gradual addition of 0.8 g (purity: 80%) of m-CPBA with ice cooling. After being stirred at the same temperature for 10 minutes, the resulting mixture was washed successively with a saturated $NaHCO_3$ solution and saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was recrystallized from acetonitrile to obtain 0.81 g of 2-(2-dimethylaminobenzylsulfinyl)-4-methylbenzimidazole as yellowish crystals. m.p. 112–114°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3200, 1480, 1440, 1420, 1290, 1040, 750

^{1}H–NMR ($CDCl_3$)δ:

2.2–2.8 (br. 3H), 2.60 (s, 6H), 4.52 and 4.84
(each d, J=13Hz, 2H), 6.7–7.6 (m, 7H)

Example 7

(1) 2-(2-Dimethylamino-6-methylbenzylthio)benzimidazole:

2-Dimethylamino-6-methylbenzyl chloride hydrochloride (4.41 g) was dissolved in 40 ml of acetone, followed by addition of 3.64 g of 2-mercaptobenzimidazole, 10 g of K_2CO_3 and 4 ml of water. The resulting mixture was stirred at room temperature for one hour. Chloroform and water were added to the reaction mixture and the chloroform layer was separated and washed with saturated brine. After drying the chloroform layer with anhydrous sodium sulfate, the solvents were distilled off under reduced pressure. The residue was crystallized from a mixed solvent of ethanol and hexane and the crystals were collected by filtration to obtain 4.68 g of 2-(2-dimethylamino-6-methylbenzylthio)benzimidazole as light brownish powder.

^{1}H–NMR ($CDCl_3$)δ:

2.42 (s, 3H,), 2.84 (s, 6H), 4.42 (s, 2H),
6.8–7.6 (m, 7H)

(2) 2-(2-Dimethylamino-6-methylbenzylsulfinyl)benzimidazole (Inventive compound 10):

2-(2-Dimethylamino-6-methylbenzylthio)benzimidazole (2.97 g) was dissolved in a mixed solvent which consisted of 30 ml of chloroform and 3 ml of methanol. With ice cooling 2.18 g of m-

CPBA (purity: 80%) was added little by little. The resulting mixture was stirred at the same temperature for 10 minutes, followed by washing first with a saturated $NaHCO_3$ solution and then with saturated brine, and thereafter dried with anhydrous sodium sulfate, followed by removal of the solvent by distillation under reduced pressure. The residue was recrystallized from a mixed solvent of chloroform and ethanol to obtain 0.75 g of 2-(2-dimethylamino-6-methylbenzylsulfinyl)benzimidazole as white crystalline powder. m.p. 141–142°C (decomposed).

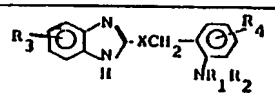
IR ν_{max}^{KBr} cm^{-1}: 3230, 1435, 1400, 1270, 1040, 740

^1H–NMR ($CDCl_3$)δ:
2.31 (s, 3H), 2.61 (s, 6H), 4.68 and
4.92 (each d, J=13Hz, 2H),
6.8–7.8 (m, 7H)

Examples 8–19

In the same manner as in Example 6 or 7, twelve compounds were further prepared, details of which are given in Table 5.

Table 5



Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
8 (Inventive compound 5)	CH_3	CH_3	5-$COOCH_3$	H	NMR ($CDCl_3$) δ ppm: 2.88 (s, 6H) 3.88 (s, 3H) 4.36 (s, 2H) 6.9-8.1 (m, 7H)	m.p. 147-148°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3175, 1725, 1490, 1425, 1290, 1080, 1040 NMR ($CDCl_3$) δ ppm: 2.62 (s, 6H) 3.94 (s, 3H) 4.48 and 4.88 (each d, J=13Hz, 2H) 6.8-8.0 (m, 7H)
9 (Inventive compound 6)	CH_3	CH_3	5-CH_3	H	NMR ($CDCl_3$) δ ppm: 2.38 (s, 3H) 2.80 (s, 6H) 4.34 (s, 2H) 6.7-7.5 (m, 7H)	m.p. 94-95°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3200, 1480, 1440, 1065, 1040, 935, 750 NMR ($CDCl_3$) δ ppm: 2.46 (s, 3H) 2.60 (s, 6H) 4.45 and 4.84 (each d, J=13Hz, 2H) 6.7-7.6 (m, 7H)
10 (Inventive compound 7)	CH_3	CH_3	5-Cl	H	NMR ($CDCl_3$) δ ppm: 2.88 (s, 6H) 4.36 (s, 2H) 6.9-7.5 (m, 7H)	m.p. 130.5-131.5°C (decomp'd) (ethanol-hexane) IR ν_{max}^{KBr} cm^{-1}: 3200, 1490, 1400, 1045, 1040, 760 NMR ($CDCl_3$) δ ppm: 2.66 (s, 6H) 4.49 and 4.83 (each d, J=13Hz, 2H) 6.7-7.8 (m, 7H)

Table 5 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
11 (Inventive compound 8)	CH_3	CH_3	5-CF_3	H	NMR ($CDCl_3$) δ ppm: 2.92 (s, 6H) 4.38 (s, 2H) 7.0-7.7 (m, 7H)	m.p. 140°C (decomp'd) (acetonitrile) NMR ($CDCl_3$) δ ppm: 2.66 (s, 6H) 4.50 and 4.88 (each d, J=13Hz, 2H) 6.8-8.1 (m, 7H)
12	CH_3	CH_3	5-NH_2	H	NMR ($CDCl_3$) δ ppm: 2.86 (s, 6H) 4.34 (s, 2H) 6.4-7.5 (m, 7H)	m.p. 146-148°C (decomp'd) (ethanol-ether) IR ν_{max}^{KBr} cm^{-1}: 3200, 1620, 1490, 1400, 1205, 1050, 760 NMR (CD_3OD) δ ppm: 2.57 (s, 6H) 4.54 and 4.79 (each d, J=13Hz, 2H) 6.6-7.4 (m, 7H)
13 (Inventive compound 11)	CH_3	CH_3	H	4-Cl	NMR ($CDCl_3$) δ ppm: 2.80 (s, 6H) 4.40 (s, 2H) 6.8-7.6 (m, 7H)	m.p. 139-140°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 1585, 1425, 1400, 1260, 1060, 950, 740 NMR ($CDCl_3$) δ ppm: 2.58 (s, 6H) 4.42 and 4.78 (each d, J=13Hz, 2H) 6.7-7.8 (m, 7H)
14 (Inventive compound 12)	CH_3	CH_3	H	5-OCH_3	NMR ($CDCl_3$) δ ppm: 2.84 (s, 6H) 3.72 (s, 3H) 4.32 (s, 2H) 6.6-7.6 (m, 7H)	m.p. 115-116.5°C (decomp'd) (ethyl acetate) IR ν_{max}^{KBr} cm^{-1}: 3200, 1495, 1400, 1280, 1245, 1150, 1020 NMR ($CDCl_3$) δ ppm: 2.60 (s, 6H) 3.50 (s, 3H) 4.47 and 4.87 (each d, J=13Hz, 2H) 6.6-7.8 (m, 7H)

Table 5 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
15 (Inventive compound 13)	CH_3	CH_3	H	5-Me	NMR ($CDCl_3$) δ ppm: 2.24 (s, 3H) 2.82 (s, 6H) 4.30 (s, 2H) 6.8-7.5 (m, 7H)	m.p. 141.5-142.5°C (decomp'd) (ethanol-hexane) IR ν_{max}^{KBr} cm^{-1}: 3220, 1600, 1410, 1270, 1045, 820, 740 NMR ($CDCl_3$) δ ppm: 2.09 (s, 3H) 2.62 (s, 6H) 4.45 and 4.84 (each d, J=13Hz, 2H) 6.9-7.8 (m, 7H)
16	CH_3	CH_3	H	3-Me	NMR ($CDCl_3$) δ ppm: 2.30 (s, 3H) 2.84 (s, 6H) 4.52 (s, 2H) 6.8-7.7 (m, 7H)	m.p. 155-156°C (decomp'd) (acetone-hexane) IR ν_{max}^{KBr} cm^{-1}: 3160, 1430, 1400, 1260, 1075, 1035, 860, 830 NMR ($CDCl_3$) δ ppm: 2.35 (s, 3H) 2.86 (s, 6H) 4.38 and 4.85 (each d, J=13Hz, 2H) 6.8-8.0 (m, 7H)
17	CH_3	CH_3	H	4-F	NMR ($CDCl_3$) δ ppm: 2.76 (s, 6H) 4.38 (s, 2H) 6.5-7.6 (m, 7H)	m.p. 118-119°C (decomp'd) (methylenechloride-acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3170, 1605, 1580, 1490, 1210, 1035, 980, 760 NMR ($CDCl_3$) δ ppm: 2.60 (s, 6H) 4.44 and 4.80 (each d, J=13Hz, 2H) 6.4-7.7 (m, 7H)

Table 5 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
18	CH_3	CH_3	5-OCH_3	6-CH_3	NMR ($CDCl_3$) δ ppm: 2.44 (s, 3H) 2.88 (s, 6H) 3.80 (s, 3H) 4.40 (s, 2H) 6.6-7.4 (m, 6H)	m.p. 143-144°C (decomp'd) (acetone-ether) IR ν_{max}^{KBr} cm^{-1}: 3220, 1440, 1190, 1140, 1035, 790 NMR ($CDCl_3$) δ ppm: 2.34 (s, 3H) 2.63 (s, 6H) 3.84 (s, 3H) 4.38 and 4.86 (each d, J=13Hz, 2H) 6.8-7.7 (m, 6H)
19	CH_3	CH_3	5-Cl	5-OCH_3	NMR ($CDCl_3$) δ ppm: 2.80 (s, 6H) 3.74 (s, 3H) 4.20 (s, 2H) 6.6-7.5 (m, 6H)	m.p. 161-162°C (decomp'd) (acetone) IR ν_{max}^{KBr} cm^{-1}: 3210, 1495, 1395, 1285, 1250, 1040, 1025, 810 NMR ($CDCl_3$) δ ppm: 2.61 (s, 6H) 3.58 (s, 3H) 4.40 and 4.82 (each d, J=13Hz, 2H) 6.6-7.8 (m, 6H)

Example 20

(2) 2-(2-Piperidinobenzylthio)benzimidazole:

To a solution of 1.42 g of 2-piperidinobenzyl chloride hydrochloride in 35 ml of ethanol were added 0.87 g of 2-mercaptobenzimidazole and 0.5 g of NaOH. The mixture was stirred at room temperature for 5 hours. The solvent was distilled off under reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The ethyl acetate solution was washed successively with a 10% NaOH solution and saturated brine. After drying the resulting solution with anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was washed with ether to obtain 1.0 g of 2-(2-piperidinobenzylthio)benzimidazole as yellow powder. m.p. 165°C.

NMR ($CDCl_3$)δ:

1.4–2.1 (m, 6H), 2.8–3.1 (m, 4H), 4.34 (s, 2H), 6.9–7.6 (m, 8H)

(2) 2-(2-Piperidinobenzylsulfinyl)benzimidazole (Inventive compound 14):

2-(2-Piperidinobenzylthio)benzimidazole (0.70 g) was dissolved in a mixed solvent which consisted of 50 ml of chloroform and 2 ml of methanol, followed by gradual addition of 1.3 g of m-CPBA (purity: 80%) with ice cooling. The resulting mixture was stirred at the same temperature for 10 minutes. Thereafter, the mixture was washed successively with a saturated $NaHCO_3$ solution and saturated brine and then dried with anhydrous sodium sulfate. The solvents were distilled off under reduced pressure and the residue was recrystallized from ether to obtain 0.45 g of 2-(2-piperidinobenzylsulfinyl)benzimidazole as white powder. m.p. 158°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3160, 1435, 1325, 1215, 1030, 920, 740

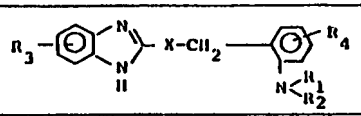
^{1}H–NMR (DMSO–d_6)δ:

1.3–1.8 (m, 6H), 2.6–2.8 (m, 4H), 4.41–4.74 (each d, J=12Hz, 2H), 6.8–7.8 (m, 8H)

Examples 21–26

In the same manner as in Example 20, six compounds were further prepared, details of which are given in Table 6.

Table 6



Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
21 (Inventive compound 15)		H	H	H	NMR ($CDCl_3$) δ ppm: 0.8-2.1 (m, 10H) 3.0-3.4 (br, 1H) 4.48 (s, 2H) 6.4-7.6 (m, 8H)	m.p. 89-92°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 2940, 1605, 1510, 1430, 1310, 1270, 1050, 750 NMR ($CDCl_3$) δ ppm: 0.7-2.1 (m, 10H) 2.9-3.3 (m, 1H) 4.35 and 4.64 (each d, J=14Hz, 2H) 6.3-7.9 (m, 8H)
22 (Inventive compound 16)		H	H	H	NMR ($CDCl_3$) δ ppm: 4.48 (s, 2H) 6.6-7.5 (m, 13H)	m.p. 89-92°C (decomp'd) (chloroform-ether) IR ν_{max}^{KBr} cm^{-1}: 3360, 1600, 1495, 1410, 1305, 1050, 750 NMR ($CDCl_3$) δ ppm: 4.47 and 4.78 (each d, J=14Hz, 2H) 6.5-8.0 (m, 13H)
23 (Inventive compound 17)		CH_3	H	H	NMR ($CDCl_3$) δ ppm: 3.18 (s, 3H) 4.40 (s, 2H) 6.4-7.6 (m, 13H)	m.p. 168-169°C (decomp'd) (chloroform-acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3050, 1590, 1485, 1400, 1260, 1055, 740 NMR ($CDCl_3$) δ ppm: 3.18 (s, 3H) 4.32 and 4.62 (each d, J=13Hz, 2H) 6.3-7.8 (m, 13H)

Table 6 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
24 (Inventive compound 18)	$-CH_2-\bigcirc$	CH_3	H	H	NMR ($CDCl_3$) δ ppm: 2.66 (s, 3H) 4.04 (s, 2H) 4.56 (s, 2H) 6.9-7.5 (m, 13H)	m.p. 137°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3170, 1440, 1400, 1260, 1025, 940, 740 NMR ($CDCl_3$) δ ppm: 2.52 (s, 3H) 4.00 (s, 2H) 4.52 and 4.92 (each d, J=12Hz, 2H) 6.7-7.9 (m, 13H)
25	$-(CH_2)_5CH_3$	CH_3	H	H	NMR ($CDCl_3$) δ ppm: 0.98 (d, J=7Hz, 6H) 1.8-2.2 (m, 1H) 2.68 (d, J=8Hz, 2H) 2.80 (s, 3H) 4.48 (s, 2H) 6.9-7.8 (m, 8H)	m.p. 121°C (decomp'd) (chloroform-hexane) NMR ($CDCl_3$) δ ppm: 0.92 (d, J=7Hz, 6H) 1.5-2.0 (m, 1H) 2.62 (d, J=8Hz, 2H) 2.64 (s, 3H) 4.52 and 4.90 (each d, J=14Hz, 2H) 6.8-7.9 (m, 8H)
26 (Inventive compound 19)	$-CH_2CH(CH_3)_2$	CH_3	H	H	NMR ($CDCl_3$) δ ppm: 0.6-2.0 (m, 11H) 2.7-3.1 (m, 2H) 2.88 (s, 3H) 4.42 (s, 2H) 6.8-7.7 (m, 8H)	m.p. 90-92.5°C (decomp'd) (chloroform-hexane) NMR ($CDCl_3$) δ ppm: 0.7-1.7 (m, 11H) 2.64 (s, 3H) 2.7-3.0 (m, 2H) 4.48 and 4.89 (each d, J=12Hz, 2H) 6.7-8.0 (m, 8H)

The following examples illustrate the use of the benzimidazole components of the invention in antiulcer agents in various forms, the effective component in each case being a compound in accordance with the invention.

Example 27
Preparation Example (Tablets):
Each tablet (220 mg) contained the following components:

Effective component	50 mg
Lactose	103 mg
Starch	50 mg
Magnesium stearate	2 mg
Hydroxypropylcellulose	15 mg

Example 28
Preparation Example (Capsules):
Each hard gelatin capsule (350 mg) contained the following components:

Effective component	40 mg
Lactose	200 mg
Starch	70 mg
Polyvinylpyrrolidone	5 mg
Crystalline cellulose	35 mg

Example 29
Preparation Example (Granules):
Each granule (1 g) contained the following components:

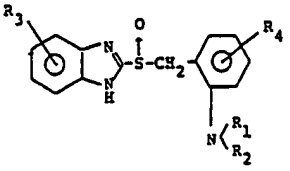
Effective component	200 mg
Lactose	450 mg
Corn starch	300 mg
Hydroxypropylcellulose	50 mg

Example 30
Preparation Example (Enteric Coated Tablets):
Each enteric coated tablet contained the components of Example 27.

The terms "lower alkyl", "lower alkoxy" and "lower alkoxycarbonyl" as used herein in the definition of groups R_3 and R_4 of Formula (I), are intended to mean alkyl and alkoxy groups having 1 to 5 carbon atoms, and alkoxycarbonyl groups in which the alkoxy moiety has 1 to 5 carbon atoms.

CLAIMS

1. A benzimidazole derivative represented by the formula (I),

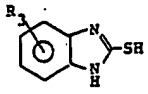


(I)

where R_1 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms, or a cycloalkyl, phenyl, or aralkyl group; R_2 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms; or R_1 and R_2 form a ring together with the adjacent nitrogen atom; and R_3 and R_4 are in each case a hydrogen or halogen atom, or a trifluoromethyl, lower alkyl, lower alkoxy, lower alkoxycarbonyl, or amino group, and may be the same or different.

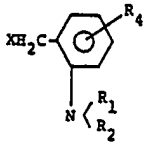
2. A benzimidazole derivative as claimed in Claim 1, substantially as hereinbefore described with reference to any of Examples 1 to 26.

3. A process for preparing a benzimidazole derivative as claimed in Claim 1, which comprises reacting a 2-mercaptobenzimidazole represented by the formula (II),



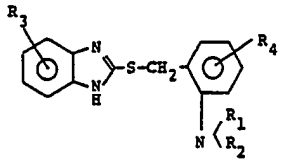
(II)

where R_3 is as defined in Claim 1, with a 2-aminobenzyl compound represented by the formula (III),



(III)

where R_1, R_2 and R_4 are as defined in Claim 1 and X is a reactive group, thereby forming a compound represented by the formula (IV),



(IV)

where R_1, R_2, R_3 and R_4 are as defined in Claim 1, and thereafter oxidizing the compound of the formula (IV).

4. A process for preparing a benzimidazole derivative as claimed in Claim 1, substantially as hereinbefore described with reference to any of Examples 1 to 26.

5. An antiulcer agent comprising as an effective component a benzimidazole derivative as claimed in Claim 1.

6. An antiulcer agent as claimed in Claim 5, substantially as described with reference to any of Examples 27 to 30.

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